Typhoid Fever and Typhoid Vaccines

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Typhoid Fever

BACKGROUND
Typhoid Fever
Etiology and Transmission

- Caused by *Salmonella enterica* serotype Typhi
  - Humans are only reservoir

- Usually acquired from contaminated food or water
Typhoid Fever
Clinical Features

- Incubation period 6–30 days
- Insidious onset
- Typical symptoms include increasing
  - Fever
  - Malaise
  - Headache
  - Anorexia
- Life-threatening complications include septic shock, intestinal hemorrhage and perforation
Typhoid Fever Treatment

- **Antimicrobials**
  - Fluoroquinolone
  - Beta-lactam
  - Azithromycin
  - Chloramphenicol
  - Trimethoprim-sulfamethoxazole

- **Antibiotic resistance common and increasing**¹

- **Case-fatality ratio for untreated disease 10-20%**,² **but <1% with appropriate antimicrobial treatment**³

¹ Crump and Mintz. Clin Infect Dis. 2010
² Stuart and Pullen. Arch Int Med. 1946
³ Bhan et al. Lancet. 2005
Enteric Fever (Including Typhoid) Etiology

- **Caused by** *Salmonella enterica* serotypes
  - Typhi → Typhoid Fever
  - Paratyphi A
  - Paratyphi B (tartrate negative)
  - Paratyphi C → Paratyphoid Fever

- Paratyphoid fever clinically indistinguishable from typhoid fever

- Current typhoid vaccines provide little or no protection against paratyphoid fever

Enteric Fever
Epidemiology—Global

- **Typhoid:** Estimated ~20 million cases annually\(^1\)
  - ~200,000 deaths/year
- **Paratyphoid:** Estimated ~5 million cases annually
  - In some Asian countries, Paratyphi A accounts for half of enteric fever cases\(^2\)
- **Multi-drug resistance** (ampicillin, chloramphenicol, and TMP-SMX) common for Typhi\(^2\)
  - Emerging fluoroquinolone-resistance and extended-spectrum β lactamase
  - Increased importance of vaccination

\(^1\) Crump et al. Bull WHO. 2004
\(^2\) Crump and Mintz. Clin Infect Dis. 2010
Typhoid Fever
Epidemiology—United States

- ~400 cases per year 2007-2011\(^1\)

- ~90% travel-associated\(^1\)
  - ~80-85% involved travel to Bangladesh, India, or Pakistan
  - Low use of vaccine among travelers (eg, ~20% of travelers received typhoid vaccine in one study) \(^2\)

- Vaccine recommendations for travel (cdc.gov/travel)
  - Travel to most countries in Africa, Asia, and Latin America
  - Since 2011, typhoid vaccine no longer recommended for travel to certain countries in Eastern Europe and the Middle East\(^3\)

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1 CDC Surveillance. [http://www.cdc.gov/nationalsurveillance/typhoid_surveillance.html](http://www.cdc.gov/nationalsurveillance/typhoid_surveillance.html)
2 Mahon et al. Vaccine. 2014
3 Johnson et al. J Trav Med. 2011
TYPHOID VACCINES
## Typhoid Vaccines Available in U.S. in 2014

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Vaccine type</th>
<th>Age</th>
<th>Mode of administration</th>
<th>No. of doses</th>
<th>Repeat dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ty21a vaccine, Vivotif®</td>
<td>Live, attenuated</td>
<td>≥6 years</td>
<td>Oral</td>
<td>4</td>
<td>Every 5 years*</td>
</tr>
<tr>
<td>Vi capsular polysaccharide vaccine (ViCPS), Typhim Vi®</td>
<td>Subunit</td>
<td>≥2 years</td>
<td>Parenteral</td>
<td>1</td>
<td>Every 2 years*</td>
</tr>
</tbody>
</table>

* No booster effect observed for either vaccine

Conjugate polysaccharide vaccines available in a few countries; not licensed in the United States
Ty21a Vaccine Efficacy

- Systematic review and meta-analysis of studies conducted in endemic countries:¹
  - 2.5–3 year cumulative efficacy was 48% (95% CI 34–58%) based on single trial
  - In 2 excluded trials that did not adjust for cluster design (and likely overestimated protective effect), efficacy was
    - 79% (95% CI 65–87%) at 5 years
    - 62% (95% CI 48–73%) at 7 years

¹ Anwar et al. Cochrane Database Syst Rev. 2014
### ViCPS Vaccine Efficacy

- **Systematic review and meta-analysis of studies conducted in endemic countries:**

<table>
<thead>
<tr>
<th></th>
<th>Efficacy</th>
<th>95% CI</th>
<th>No. trials included</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1</td>
<td>69%</td>
<td>63–74%</td>
<td>3</td>
</tr>
<tr>
<td>Year 2</td>
<td>59%</td>
<td>45–69%</td>
<td>4</td>
</tr>
<tr>
<td>Cumulative 2.5–3 years</td>
<td>55%</td>
<td>30–70%</td>
<td>1</td>
</tr>
</tbody>
</table>

1 Anwar et al. Cochrane Database Syst Rev. 2014
Typhoid Vaccination
Effectiveness in travelers

- No efficacy studies among US travelers

- 80% (95% CI 66–89%) effectiveness of typhoid vaccination among US travelers
  
  Estimate is for any typhoid vaccination—not able to differentiate between vaccines

1 Mahon et al. Vaccine. 2014
Typhoid Vaccines
Safety Data

- Both vaccines generally well-tolerated with low rates of adverse events
  - Data from trials and post-marketing studies
Ty21a Vaccine Safety Data

- In meta-analysis of field trials, certain events more common in vaccinees than placebo recipients:\(^1\)
  - Fever (RR 1.8, 95% CI 1.0–3.1)
  - Combined any mild adverse event (RR 1.7, 95% CI 1.0–2.7)

- Estimated 0.6 serious events reported per 100,000 doses distributed\(^2\)
  - Vaccine Adverse Events Reporting System (VAERS) data
  - Serious adverse events defined as reports of death, hospitalizations, prolongation of hospitalization, permanent disability, life-threatening illness, or congenital anomaly

\(^1\) Anwar et al. Cochrane Database Syst Rev. 2014
\(^2\) Begier et al. Clin Infect Dis. 2004
ViCPS Vaccine Safety Data

- In meta-analysis of field trials, symptoms more common than placebo:
  - Pain (RR 8.0, 95% CI 3.7–17.2)
  - Swelling at injection site (RR 6.0, 95% CI 1.1–34.2)

- Estimated 0.3 serious events reported per 100,000 doses distributed
  - Vaccine Adverse Events Reporting System (VAERS) data
  - Serious adverse events defined as reports of death, hospitalizations, prolongation of hospitalization, permanent disability, life-threatening illness, or congenital anomaly

1 Anwar et al. Cochrane Database Syst Rev. 2014
Typhoid Vaccines
Contraindications

- **Ty21a and ViCPS:** hypersensitivity to any component of vaccine\(^1,2\)

- **Ty21a**
  - Live bacterial vaccines generally contraindicated in pregnant women\(^3\)
  - Contraindicated in immunocompromised persons\(^1\)
  - Should not be administered during acute febrile illness\(^1\)

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3. ACIP. General Recommendations on Immunization. 2011
Typhoid Vaccines
Precautions

- **Ty21a:** Avoid antimicrobial agents, if possible, 3 days before and after vaccine administration\(^1\)
  - Certain anti-malarial prophylaxis medications can be taken at same time as vaccine\(^1\)
  - Can be co-administered with other live vaccines\(^2\)

- **ViCPS:** Should be given to pregnant women only if clearly needed\(^3\)

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2. ACIP. General Recommendations on Immunization. 2011
Typhoid Vaccines

PROPOSED UPDATES TO RECOMMENDATIONS
Proposed Recommendation (1)
Typhoid Vaccine Indicated For

- “Travelers to areas in which there is a recognized risk of exposure to Salmonella serotype Typhi (see cdc.gov/travel/)
  - “Risk is greatest for travelers to developing countries (e.g., countries in Latin America, Asia, and Africa) who have prolonged exposure to possibly contaminated food and drink, although short-term travelers are also at risk.
  - “Multidrug-resistant strains of Salmonella serotype Typhi have become common in many regions, and cases of typhoid fever that are treated with drugs to which the organism is resistant can be fatal.
  - “Travelers should be cautioned that typhoid vaccination is not a substitute for careful selection of food and drink. Typhoid vaccines are not 100% effective, and vaccine-induced protection can be overwhelmed by large inocula of Salmonella serotype Typhi.”

- No substantive changes to 1994 recommendation
Proposed Recommendation (2)
Typhoid Vaccine Indicated For

- “Persons with intimate exposure (e.g., household contact) to a documented Salmonella serotype Typhi chronic carrier (defined as excretion of Salmonella serotype Typhi in urine or stool for >1 year)”

- Change to 1994 recommendation
  - Carrier specified as “chronic”
  - Chronic carriage defined (excretion >1 year)
Proposed Recommendation (3) Typhoid Vaccine Indicated For

- “Microbiologists and laboratory workers who work with cultures of Salmonella serotype Typhi or with specimens that contain this organism or who work in laboratory environments where these cultures or specimens are handled.”

- 1994 recommendation
  - “Microbiology laboratorians who work frequently with S. typhi”
Proposed Recommendation
Choice of Vaccine

- “Parenteral Vi polysaccharide and oral Ty21a vaccines are both acceptable forms of typhoid immunization”

Consider
- Approved ages for use
  - ≥6 years for Ty21a
  - ≥2 years for ViCPS
- Dosing
  - 4 oral capsules on alternating days for Ty21a
  - Single injection for ViCPS
- Contraindications and precautions

- The inactivated whole cell vaccine that is no longer available has been deleted from the recommendation
Summary

- 1994 ACIP typhoid vaccines statement outdated
- No substantive changes in recommendations proposed
- Updated statement reflects
  - Change in vaccine availability (whole-cell vaccine discontinued)
  - Newer data on typhoid epidemiology
  - Newer data on vaccine efficacy and safety
Questions and Discussion

For more information please contact Centers for Disease Control and Prevention

1600 Clifton Road NE, Atlanta, GA 30333
Telephone: 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348
Visit: www.cdc.gov | Contact CDC at: 1-800-CDC-INFO or www.cdc.gov/info

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